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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,021	03/19/2002	Philippe Gabant	VANM243.1APC1	5739

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EXAMINER	
NGUYEN, DAVE TRONG	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,021	GABANT ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,6,7 and 9-18* is/are pending in the application.

4a) Of the above claim(s) *9 and 11-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 6, 7, 10, 14, and 15-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January Feb 8, 2005 has been entered..

Claims 1, 2, 6, and 10 have been amended, and claims 16-18 have been added by the amendment filed Feb. 8, 2005

Claims 1, 4, 6, 7, 9-18 are pending.

Claims 9, 11-13 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention. A complete response to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) MPEP 821.01.

Claims 1, 4, 6, 7, 10, 14, and 15-18, to which the following grounds of rejection remain and/or are applicable, are pending for examination.

Claims 1, 4, 6, 7, 10, 14-15 remain, and claims 16-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification is only enabling for claims limited to:

1/ A genetically modified female mouse, whose genome comprises a homozygous mutation, a partially homozygous deletion or a totally homozygous deletion in the endogenous genetic sequence encoding the wild- type alpha-fetoprotein (AFP),

wherein said genetically modified female mouse does not express a functionally active AFP, is sterile, and does not undergo a menstrual cylclization; and

2/ A method for identifying a candidate agent for use in treating osteoporosis, increasing fertility, or preventing conception comprising:

contacting the genetically modified female mouse of 1/ with a candidate agent;

determining the effects of said agent on osteoporosis, fertility or conctraception in said genetically modified female mouse.

The specification is not enabling for claims directed to any other claimed embodiment within the elected claimed invention. The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

As set forth in the previous office action, the main thrust of the claimed invention is applicant's discovery of a nexus between a murine AFP and its role for female production and fertility (page, 3, par. 006). This discovery was based on the making of

AFP knock-out mice (par. 008, working examples, wherein recombinant ES cells carrying the targeted allele were injected in C57BL/6J blastocysts (par. 0019), and wherein both heterozygous embryos and homozygous embryos/mice were produced. As the result of the making of these AFP knock-out mice, and further intercrosses, applicant observed and concluded, particularly on the basis of AFP knock out homozygous mice and their subsequent intercrosses (page 9), that no pugs were obtained from this intercrosses, thereby suggesting an essential role of AFP for development and/or fertility (Table 2). Page 9 further states that "males homozygous for an *afp* disrupted allele appeared fertile and sired offspring but homozygous females never produce any live offspring". An histological analysis was done on the AFP knock out homozygous females (*afp* $^{lacZ1/lacZ1}$) shows that (page 10) their homozygous tissues do not contain corpus lutea, the lack of which is indicative of the absence of ovulation (Figure 4). On the basis of this finding, Applicant further suggests on page 14 that "the *afp-/-* phenotype corresponds to alive sterile females, which is a phenotype that may exist in the mouse population as well as in the human population. However, the claims as currently pending do not reflect such claimed embodiment. The claims still embrace a sterile female genetically modified mouse, wherein the mutated, deleted, or partial deleted APF could still be expressed, and/or wherein only a heterozygous mutation, partial deletion, or a total deletion in one of the alleles, which contains the endogenous genetic sequence encoding the AFP. New added claims appear to be even broader, wherein the claimed mouse do not even require any particular structure, *e.g.,* a partial deletion or a total deletion in each allele of endogenous genetic sequence encoding the

wild type AFP. As set forth above, one of the essential element of the claimed invention is that the AFP protein must not be expressed as the result of a mutation or deletion of the endogenous AFP homozygously, and that only such essential element once achieved would cause sterility in female mice. As such, the claimed invention must necessarily require that AFP protein is null or non-expressible so as to disrupt the ovulation in the treated mice. Otherwise, it would require an undue experimentation for a skilled artisan to make and use the claimed invention as broadly claimed, whereby AFP is expressible and yet not functional and/or expressed at an insufficient level (see claims 16-18), and yet the treated mouse is sterile as the result of the genetic modification in endogenous AFP coding sequence. Another issue is that the claimed invention as currently pending does not recite that the genome of the claimed mouse comprises a homozygous mutation, a partially homozygous deletion or a totally homozygous deletion in the endogenous genetic sequence encoding the wild- type alpha-fetoprotein (AFP). In fact, claim 14 claims a genetically modified mouse, which is heterozygous for a mutation, a partial deletion or a total deletion in the endogenous genetic sequence encoding the wild type alpha-fetoprotein (AFP). However, there is no evidence that any useful phonotype can be effected by such a heterozygous AFP/- mouse. In fact, the specification on page 7 states that "phenotypically normal heterozygous mice *afp lacZ1/+* were generated and detected by Southern blot (see figure 1C)". Furthermore, the state of the art of transgenics is such that while one skilled in the art can disrupt a gene in mouse ES cells and produce a subsequent transgenic mouse by using the cloned ES cells, it is not reasonably predictable for one

skilled in the art to produce a transgenic mouse that exhibits a desired phenotype, wherein the mouse has not been actually produced with a contemplated phenotype. In this instance, nowhere in the specification a reasonable skilled artisan could find any evidential support to demonstrate that a desired phenotype was generated as the result of a heterozygous AFP knock mouse. At the time the invention was made, the art of transgenics including gene targeted modification by using ES cell technology or any *in vivo* gene manipulation protocol was known to be unpredictable with respect to the efficacy of incorporation of transgene, levels of expression as a result of the incorporation, and the phenotypes expressed as a result of the transgene incorporation via homologous recombination in ES cells (Polejaeva *et al.*, Theriogenology, Vol. 53, pages 117-126, 2000; & Sigmund, 2000, Thromb Vasc Biol., 20:1425-29). More specifically, Polejaeva *et al.* states:

> Transgenic animals can be successfully produced in a number of species including mice, rabbits, pigs, sheep cattle, and goats by the injection of the gene of interest into the pro-nucleus of a zygote. However, this technique suffers from several serious limitations. The most profound is that DNA can only be added, not deleted, or modified in situ. Also, the integration of foreign DNA is random; this could lead to erratic transgene expression due to the effects at the site of incorporation. In addition, with random integration the possibility exists for the disruption of essential endogenous DNA sequences or activation of cellular oncogenes, both of which would have deleterious effects on the animal's health. Finally, transgenic animals generated using pro-nuclear microinjection are commonly mosaic, i.e., an integrated transgene is not present in all cells. Therefore, the production of the required phenotype coupled to germ line transmission could undue experimentation. See page 119.

In addition, Rulicke (Experimental Physiology, 85, 6:589-601, 2000), states that "the overall phenotype of a transgenic organism is influenced by several genetic and

environmental factors", and that "due to the features of this technique not all of the genetic factors can be experimentally controlled by the scientist" (abstract).

With respect to the lack of predictability in assessing a product of a transgenic animal, Rulicke states on page 596 bridging page 597:

> There is continuous and remarkable development in transgenic technology, particularly in the quality of transgenes and experimental approaches. Nevertheless, the consequences of experimentally induced mutations cannot be completely predicted. Even although our experience shows that the welfare of the majority of transgenic animals is not noticeably affected, randomly integrated foreign DNA may increase the risk of disturbing the normal physiology of animal. The resulting phenotypic changes may be crucial to the animals' welfare already during breeding and maintenance of a transgenic line. Apparent and relevant phenotypic changes can only be determined after a careful and comprehensive assessment (Merten & Rulicke, 1999, 2000). This monitoring for phenotypic changes should be done as early as possible, namely during the establishment of a new transgenic line. Since each transgenic line produced by pronuclear injection is unique, it has to be carefully assessed separately by specialists.

Notwithstanding numerous unpredictable and yet unknown factors in assessing a phenotype of a transgenic mouse, Bamptom, Brain Research, Vol. 841, 123-134, 1999, states that "transgenic or knockout mouse models provide the opportunity to study the function of disease-related or novel genes, that "[H}however, a confounding factor in all such research is the genetic and phenotypic variation of the mouse strain used to construct the models", and that "since production of a transgenic or knock-out mouse frequently requires cross-breeding, care should be taken in establishing the contribution of parent strains to the final phenotype, as well as the potential interaction with the phenotype arising from the knock-out transgene" (abstract), page 123 bridging page 124.

The doubts expressed by the art of record, thus, are especially true for the majority of transgenic animals that are generated by pronuclear injection. Given the doubts expressed by the art of the record, the breadth of the claims, the lack of working examples and/or guidance in showing a reasonable correlation to that of the current breadth of the claims, and particularly the nature of the invention and its associated unpredictable factors in assessing a phenotype of a transgenic product, it is not apparent as to how one skilled in the art, without any undue experimentation, makes and uses genetically modified mice other than those as disclosed in the enabling embodiments, particularly on the basis of applicant's disclosure. As such, the claims are only reasonably enabling for claimed directed to the embodiments as indicated in the first paragraph of the stated rejection.

Applicant's response (pages 4-6) has been considered by the examiner fully, but is not found persuasive for the reasons as set forth in above stated rejection. More specifically, Applicant asserts on page 4 that the invention as pending is analogous to that of *Hybritech Inc. v. Monoclonal Antibodies,* however, the two are distinct because protocols in making monoclonal antibodies are not the same as that of the claimed invention. The evidence as illustrated in the stated rejection speaks for itself. Note that there is no evidence from any prior art of record to substantiate the analogy. Applicant further cites the accompanying declaration and the guidance provided by the as-filed specification, which state that there are many techniques for modifying the mouse genome known in the prior art. However, simple existing techniques for studying and/or modifying the genome of a mouse, or even citation of other know transgenic mice drawn

to another distinct knock-out gene, are not the same as the ability of a skilled artisan to reasonably predict the outcome or phenotype of a transgenic mouse having a particular gene targeted for knockout (let alone controlling the level of gene expression as contemplated in claim 18, for example) as the result of employing any existing cloning technique, *e.g.,* nuclear injection, somatic cloning, and ES cloning technology. Neither applicant's response nor applicant's Declaration are sufficient to properly rebut the doubts expressed in the art of record, the lack of commensurate working examples, and particularly the broad scope of the claimed invention. Applicant 's assertion on the last paragraph of page 5 bridging page 6 also has been considered but is not found persuasive because there is no evidence to overcome the fact that heterologous mice carrying one copy of an AFP mutation do not necessarily possess any of the claimed phenotypes, and as such, the same conclusion can be reasonably concluded for their offspring arisen from crossings, which include those having both alleles of the AFP gene modified, particularly since there are my variable factors, *e.g.,* random gene integration, a particular mutation of the AFP gene, as shown in the art of record, which would effect the phenotypic changes of the transgenic mice, and thus, the consequences of experimentally induced mutations cannot be completely predicted for the heterologous mice, let alone the homozygous offspring arisen from the crossings.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **571-272-0731**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Ram Shukla*, may be reached at **571-272-0735.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Central Fax number, which is **571-273-8300**.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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